Articles

Increased risk of Alzheimer's disease in mothers of adults with Down's syndrome

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Summary

Most adults with Down's syndrome (DS) develop neuropathology characteristic of Alzheimer's disease (AD) by the age of 40. Most of the non-dysjunction events in DS are of maternal origin. We postulated therefore that a shared genetic susceptibility to DS and AD would be associated with an increased frequency of AD among mothers, but not fathers, of individuals with DS. We further hypothesised that the shared susceptibility could involve an accelerated ageing process, leading to the birth of a child with DS to a relatively young mother and to an increased risk of dementia in the mother and her relatives.

Families of 96 adults with DS and of 80 adults with other forms of mental retardation were ascertained through the New York State Developmental Disabilities services network. A semi-structured interview was used to obtain information on the presence or absence of non-stroke-related dementia and other disorders in parents. There was an increase in risk of dementia among mothers of DS probands compared with control mothers (risk ratio 2·6 [95% CI 0·9–7·3]). The risk of dementia among mothers who were 35 or younger when their DS children were born was 5 times that of control mothers (4·9 [1·6–15·4]). There was no increase in risk of dementia among mothers who were older (>35 years) at the proband's birth (0·8 [0·2–3·4]). There was no difference in risk of dementia between fathers of DS cases and fathers of controls (1·2 [0·4–3·9]) and no discernible influence of age on this risk.

Familial aggregation of dementia among mothers of adults with DS supports the hypothesis of a shared genetic susceptibility to DS and AD.

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Introduction

Virtually all adults with Down's syndrome (DS) older than 40 years have brain morphology similar to that of Alzheimer's disease (AD) cases,[1,2] which suggests a shared genetic susceptibility to DS and AD. Studies of familial aggregation show an increased frequency of DS births in the families of individuals with AD and an increased frequency of AD in relatives of DS subjects. The EURODEM collaborative re-analysis of case-control studies found that the odds of developing AD were 2·7 times higher for a subject who had a first-degree relative with DS than for subjects who had no DS relative.[3] However, of thirteen studies of the association between DS and AD,[4-16] only four have reported a significant relation.[4,6,11,14] All but two[11,13] of these studies examined the frequency of DS birth, a rare event, among relatives of patients with AD and among relatives of controls; most analyses therefore lacked sufficient statistical power to detect the association.

In 95% of DS trisomies, the non-dysjunction event is of maternal origin.[17,18] Thus, if there is shared genetic susceptibility to DS and AD, the frequency of AD should be increased among mothers, but not fathers, of individuals with DS. However, no study so far has examined the association between parental origin of trisomy 21 and risk of AD.

After age 35, the risk of bearing a child with DS increases greatly with increasing maternal age.[19,20] Thus, for mothers over 35 years old, the greater risk of bearing a child with DS may be influenced primarily by normal ageing. In younger mothers, however, a susceptibility factor, perhaps involving an accelerated ageing process, could lead both to the birth of a child with DS and to an increased risk of AD in the mother. That is, perhaps a woman who gives birth to a child with DS before she is 35 is biologically older than her chronological age, which would raise the risks of both trisomy and AD. This model of accelerated ageing implies that there may be a shared genetic susceptibility for an earlier age at trisomy and an earlier age at onset of AD. We therefore hypothesised that mothers who gave birth to DS children when they were 35 or younger would have an increased frequency of AD.

Data for this study were collected as part of the Family Health Study of the New York State Institute for Basic Research in Developmental Disabilities. We compared the frequency of AD in the parents of adults with DS and in parents of adults with other forms of mental retardation. We postulated an increased frequency of dementia among mothers who were 35 or younger compared with mothers who were older than 35 when their children with DS were born and compared with mothers of individuals with other forms of mental retardation. Fathers of adults with DS were not expected to have an increased risk of dementia.

Subjects and methods

Adults with mental retardation, residing in the nine-county downstate region of New York, were identified through the Developmental Disabilities Profile, a computerised database maintained by the New York State Office of Mental Retardation and Developmental Disabilities, supplemented by an independent survey of all state and voluntary service providers used in a previous study (W B Zigman, principal investigator) to develop a registry of persons with DS in New York State. The first group (DS probands) consisted of a random sample of adults with DS, aged 30–69 years, and the control group consisted of probands with other forms of mental retardation (autism, cerebral palsy, epilepsy, mental retardation, and other neurological impairments) frequency-matched to the DS probands for age, sex, and severity of mental retardation. We chose these developmentally disabled individuals and their parents as the control group to allow for non-specific factors associated with significant lifelong impairment in a family member and because we expected that ascertainment procedures, rates of participation, and recall bias would be similar to those of DS probands.

Families of the probands were contacted with the help of the responsible service provider agencies. To avoid selective participation of families with a history of dementia, the study was described as a survey of age-related diseases in individuals with developmental disabilities and their families. Probands without first-degree relatives and who had no contact with second-degree relatives were ineligible (28%; no difference between groups). Participation rates among eligible families were 72% for DS families and 64% for control families. We report here on parents' history of dementia in 96 families of adults with DS and 80 families of adults with other forms of mental retardation.

A semi-structured interview was used to collect information about DS and control probands and to confirm information provided on the Developmental Disabilities Profile database. We interviewed a caregiver of the proband (direct-care staff or staff supervisor) at the relevant residential or day-treatment facility. Interviewers were unaware of our main hypotheses. The interview obtained information on age, sex, race, aetiological and functional diagnosis, and medical history. Medical records were reviewed to validate information obtained on interview.

We attempted to interview more than one informant in each family to increase the sensitivity of the family histories. The mean number of informants was 1·9 for DS families (range 1–4) and 1·6 (1–5) for control families. We used a semi-structured family history questionnaire for AD and other common age-related neurological and medical disorders. Interviewers were again unaware of our hypotheses and also of the case/control status of the family.

The family history questionnaire asked for a list of all first-degree and second-degree relatives, their vital status, date of birth, birth order, level of education, current age or age at death, and cause of death. Family medical history was investigated by questions on the presence or absence of dementia and several common age-related medical conditions. As well as direct questioning on the history of dementia, senility, hardening of the arteries, AD, or other mental changes, we asked five screening questions on memory loss, difficulty in activities of daily living, and confusion or disorientation. A supplementary questionnaire was used to provide detailed information on dementia symptoms and age at onset for individuals who were reported positive on any direct or screening question. That questionnaire also covered history and age at onset of stroke, alcoholism, psychiatric disorders, seizures, syphilis, and other disorders that might result in dementia. The operational criteria applied to the responses to the supplementary questionnaire to arrive at a diagnosis of primary degenerative dementia included a history of progressive memory loss, confusion and disorientation, and difficulty with activities of daily living, such as dressing and eating. Parents were classified as affected if progressive memory loss and one or more other symptoms in these categories were reported. For diagnosis of dementia in parents, the operational criteria for diagnosis were applied to the information from each family informant separately. If there was disagreement among informants, priority was given to spouses, then offspring, parent's sibling, and spouse's sibling. If other medical disorders that might result in dementia were reported or the responses were ambiguous, the study neurologist (RM) assessed each case separately, using information from all informants, while unaware of the case or control status. Three models with these criteria were tested: (a) all parents who met the operational criteria were taken to be affected, irrespective of the aetiology of the dementia; (b) parents who had suffered a stroke that preceded the onset of dementia were taken to be unaffected, as were parents with a history of other medical disorders that might result in dementia (n = 13); and (c) the parents who had suffered a stroke that preceded the onset of dementia or who had a history of other medical conditions that might result in dementia were excluded from the analysis (n = 13). The same pattern of results was obtained with all three models and we present the detailed results from the second, most conservative, model.

We used t and χ^2 tests to compare demographic characteristics of DS and control probands and their parents. Reliability of family history information was assessed by kappa statistics for the history of dementia and product-moment correlation coefficients for age at onset, combining case and control families.[21] We used survival methods to assess the parental risk of AD. We estimated the cumulative incidence of dementia by a "reconstructed cohort" design[22] in which each parent was taken to be at risk of AD from birth until current age or age at death (if unaffected) or age at onset of dementia. Life-table methods were used to estimate cumulative incidence of dementia among case and control parents. These analyses were repeated within strata defined by parent's age at DS birth (≤ 35 *vs* > 35 years), since this is the age by which a woman's risk of bearing a child with DS has clearly increased. Separate analyses were done for mothers and fathers. Univariate and multivariate Cox's proportional-hazards models were then used to calculate rate ratios for dementia in mothers and fathers of DS probands compared with mothers and fathers of probands with

	DS	Control
Probands		
n	96	80
Age (yr)*	47 9 (9 3)	50 3 (10 3)
M/F†	46 (48)/50 (52)	41 (51)/39 (49)
Level of mental retardation†		
Mild/moderate	37 (39)	27 (34)
Severe	41 (43)	37 (46)
Profound	18 (19)	16 (20)
Parents		
n	184	151
Age (yr)*		
Mothers	72 8 (11 2)	71 4 (11 7)
Fathers	71 3 (10 5)	69 2 (14 4)
Age at proband birth (yr)*		
Mothers	32 9 (7)	27 8 (6)‡
Fathers	35 8 (8)	32 9 (8)‡
Education less than high school†		
Mothers	35 (38)	44 (58)‡
Fathers	39 (42)	31 (43)

*Mean (SD). †No (%). ‡$p < 0$ 05.

Table 1: **Proband and parent characteristics**

	All parents	Demented	Cumulative risk to age 85 (SE)	Rate ratio (95% CI)*
Mothers				
Probands with DS	95	17	0 27 (0 076)	2 6 (0 9–7 3)
≤35 yr at birth	58	13	0 39 (0 109)	4 9 (1 6–15 4)
>35 yr at birth	37	4	0 09 (0 062)	0 8 (0 2–3 4)
Controls	77	5	0 10 (0 048)	1 0
Fathers				
Probands with DS	93	8	0 15 (0 070)	1 2 (0 4–3 9)
≤35 yr at birth	47	4	0 17 (0 117)	1 1 (0 3–4 3)
>35 yr at birth	44	4	0 13 (0 071)	1 4 (0 4–5 4)
Controls	74	5	0 12 (0 059)	1 0

*Adjusted for age and education.

Table 2: **Cumulative incidence and rate ratio of dementia in parents of DS probands and of control probands (with other forms of mental retardation)**

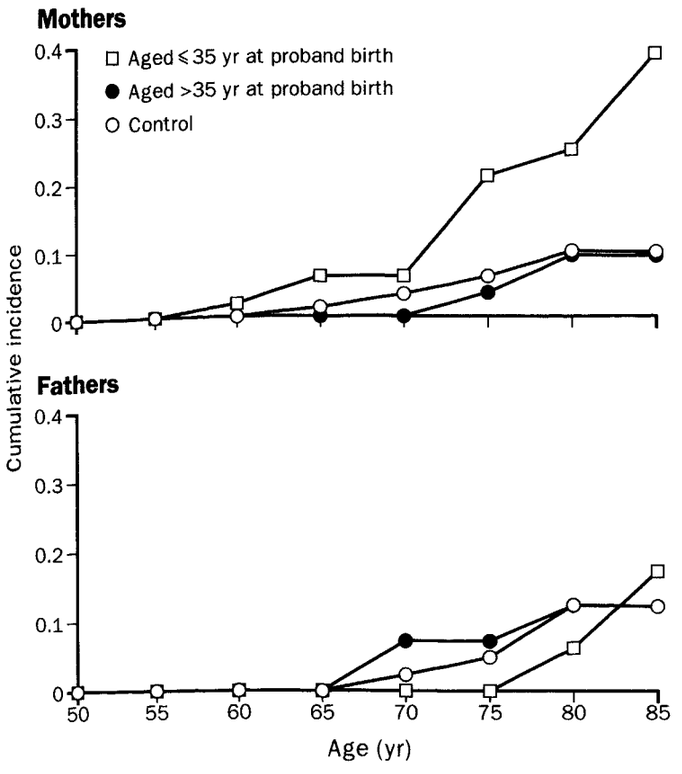

Figure: **Cumulative incidence of dementia in parents of adults with DS and of adults with other forms of mental retardation.**

other forms of mental retardation, after adjustment for age and education.[23] The final analyses compared mothers who were 35 or younger at the birth of their DS children with all control mothers, and mothers who were older than 35 when their children with DS were born with all control mothers. This analysis was repeated for fathers. All analyses used BMDP/386 Dynamic software.

Results

DS and control probands did not differ in age, sex distribution, or level of mental retardation (table 1). Parents of DS probands did not differ from those of control probands in current age or age at death, but as we expected, both mothers and fathers of DS probands were significantly older at proband birth than the corresponding control parents. More mothers of probands with DS had completed high school education than had mothers of controls ($p < 0.05$), but the level of education did not differ between DS and control fathers.

54% of the parents had one informant and the remaining 46% had two or more informants. Informants were first-degree relatives or spouses for 83% of the parents and more distant relatives for the remaining 17%. The proportion of informants who were first-degree relatives or spouses was the same for parents of cases and parents of controls, and for fathers and mothers. Agreement between pairs of family informants on the history of dementia ranged from "substantial" to "almost perfect" ($0.65 \leq \text{kappa} \leq 1.0$) when both informants were first-degree relatives or spouses of the parent; however, agreement was only "fair" for one first-degree and one second-degree relative (kappa = 0.38). The correlation coefficient for age at onset of dementia ranged from 0.93 to 1.0 for pairs of first-degree relatives of the parent and was 0.80 for pairs of first-degree and second-degree relatives.

We had no information on age, age at onset, or history of dementia for 1 mother and 3 fathers of DS probands and for 3 mothers and 6 fathers of controls. 17 (18%) mothers of DS probands and 5 (7%) controls' mothers were reported to be affected with dementia. Among fathers the corresponding numbers were 8 (9%) and 5 (7%). Thus, there was an increase in risk of dementia among mothers of DS probands ($p = 0.06$, table 2) but not among fathers ($p = 0.72$).

Within strata defined by parental age at DS birth, the risk of dementia among mothers who were 35 or younger when their children with DS were born was 5 times that of control mothers ($p = 0.003$; table 2, figure). By contrast, the risk of dementia among mothers who were older than 35 when their children with DS were born was similar to that of control mothers ($p = 0.52$). Among fathers of DS cases and controls, risk of dementia did not vary by age at proband birth.

Discussion

This study provides clear evidence of familial aggregation of DS and AD. The design used provides greater power to detect familial aggregation than most previous studies because we examined histories of the more common disorder (AD) among parents of adults with the rarer disorder (DS).

The study was specifically designed to investigate the risk of AD in relatives of DS probands, taking into account the probable parental origin of the trisomy 21 and the parental age at birth of the DS child. In our study, mothers who were 35 or younger at the time of proband birth were at increased risk of dementia. We suggest that the mixed results of previous studies are due to a dilution of the at-risk pool by inclusion of paternal relatives and relatives of mothers who were older than 35 years at DS birth, who do not have an increased risk of AD. Our results are consistent with evidence that 95% of DS trisomies are associated with a non-dysjunction event in maternal gametes.[17,18] Our finding that familial aggregation of DS and AD depends on young maternal age at proband birth supports the hypothesis that DS and AD share a genetic susceptibility related to accelerated ageing. Heston et al,[4] who studied AD patients as the probands, noted that in their families DS birth was associated with early age at onset of AD in the proband and relationship to the proband through the maternal line; these findings are further evidence for this interpretation of our results.

One limitation of our study is the lack of information on DS karyotype. Because the DS probands are all older than 30 years, even the youngest were born before karyotypes were available. Data on the prevalence of different DS karyotypes at birth suggest that we could expect full trisomy in 95% of DS probands, mosaic DS in 2–3%, and a translocation involving chromosome 21 in 3–4%.[24] Mosaicism results primarily from non-dysjunction in somatic, not germ, cells, and its occurrence would not change the estimate of shared risk of DS and AD. The occurrence of translocation DS in probands, however, might reduce the association between DS and AD, because our hypothesis specifies that accelerated ageing results in a non-dysjunction event leading to full trisomy; translocation DS thus arises from a different mechanism. Since translocation DS is more frequent among children of younger mothers,[25] the true maternal age effect in the association between DS and AD may be even greater than we observed. This dilution of the association would be expected whether the translocation was de novo or the result of a balanced rearrangement involving chromosome 21 in the mother.

A final implication of our results is that a family history of AD may constitute a risk factor for a DS birth in younger

women. There are no known risk factors for DS birth at a young age, although most DS births are to women under age 35, because of their higher fertility rates. Studies should investigate whether a maternal family history of AD can provide useful information for improving primary prevention of DS. In addition, the relation we have found between trisomy 21 and AD may hold for trisomies of other autosomal chromosomes. This association would not be observed in cases ascertained among livebirths because almost all trisomies other than DS are lethal in utero.[26] Trisomies constitute 3% of all pregnancies.[26] If there is a relation between all autosomal trisomies and risk of AD, the number of individuals with the postulated susceptibility factor in the population may be greater than expected from examination of the increased risk of AD only in mothers of individuals with DS.

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